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EXAMINER	
SASAN, ARADHANA	

ART UNIT	PAPER NUMBER
1615	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,629	JEPSEN, SVENN KLUVER	
	Examiner	Art Unit	
	ARADHANA SASAN	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *12-20,22-25,31 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,21 and 26-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/19/05 and 6/13/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Restriction Response

1. Applicant's election with traverse of Group I (claims 1-11, 21 and 26-30) in the reply filed on August 5, 2008 is acknowledged.

The traversal is on the ground(s) that the restriction is based on a finding that the recited oral pharmaceutical formulations are not patentable over the prior art. Applicant argues that while the Office Action cites WO 81/02671 for teaching a composition comprising a granulate of mesalazine, the cited reference does not teach or suggest a granulate comprising more than 60% by weight of mesalazine or a pharmaceutically acceptable salt thereof, as recited in the instant claims. Applicant argues that at page 11, WO 81/02671 teaches the use of 250 g of mesalazine (5-ASA) to make 650 g of granulate, so that the granulate comprises less than 40% by weight mesalazine.

This is not persuasive because instant formulation claims 1-10 do not present a contribution over the prior art. Although the granulate disclosed in WO 81/02671 (Page 11) comprises 38.46% by weight mesalazine (calculated 250mg/650mg=38.46%), one of ordinary skill in the art would find have found it obvious at the time the invention was made to modify the loading of the mesalazine in the granulate composition during the process of routine experimentation and arrive at the instantly claimed granulate comprising more than 60% by weight of mesalazine. Therefore, the instant formulation claims 1-10 lack an inventive step over the prior art (Page 11, lines 15-23, Preparation of granulate I). As a result, as currently presented, the instant formulation claims do not share a special technical feature with the instant method claims 12-20, 22-25 and 31-32

and, as such, unity between the above Groups I - II is broken. Therefore, the technical feature linking the inventions of groups I-II does not constitute a special technical feature as defined by PCT Rule 13.2 as it does not define a contribution over the prior art.

The restriction requirement is still deemed proper and is therefore made FINAL.

2. Claims 12-20, 22-25 and 31-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

3. Claims 1-11, 21 and 26-30 are included in the prosecution.

Information Disclosure Statement

4. The information disclosure statements (IDS) submitted on 10/19/05 and 06/13/07 are acknowledged. The submissions are in compliance with the provisions of 37 CFR 1.97 and 1.98. Accordingly, the examiner is considering the information disclosure statements.

See attached copy of PTO-1449.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-3 and 7-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Villa et al. (WO 00/76481 A1).

The claimed invention is an oral pharmaceutical formulation in the form of a granulate comprising more than 60% by weight of mesalazine or a pharmaceutically acceptable salt thereof.

Villa teaches controlled release oral pharmaceutical compositions containing as active ingredient 5-amino-salicylic acid (5-ASA), also named mesalazine (Page 1, lines 1-3). The composition comprises an inner lipophilic matrix in which the active ingredient is at least partially inglobated, an outer hydrophilic matrix in which the lipophilic matrix is dispersed an optionally other excipients (Page 4, lines 1-8). "The weight content of the active ingredient in the lipophilic matrix usually ranges from 5 to 95%" (Page 5, lines 9-10). "The compositions of the invention can contain a high percentage of active ingredient compared with the total composition weight up to 95%, an advantageous characteristic in the case of mesalazine which requires rather high unitary doses" (Page 6, lines 15-19). Example 1 discloses 5-ASA at 91.67% (calculated 770g/840g = 91.67%) of the total granulate (Page 7, lines 4-27).

Regarding instant claims 1-3, the limitations of an oral pharmaceutical formulation in the form of a granulate comprising more than 60% by weight of mesalazine, more than 70% by weight of mesalazine and more than 80% by weight of mesalazine are anticipated by the composition with a weight content of active such as 5-ASA or mesalazine at 5 to 95% and in particular by the example of 91.67% of mesalazine in the granulate, as taught by Villa (Page 5, lines 9-10 and Page 7, lines 4-27).

Regarding instant claim 7, the limitation of the pharmaceutical formulation further comprising a pharmaceutically acceptable binder is anticipated by the 30g of Carbopol (calculated weight %: 30g/1000g = 3%) and 65g of hydroxypropylmethylcellulose (calculated weight %: 65g/1000g = 6.5%) used by Villa (Page 7, lines 5-11).

Regarding instant claim 8, the limitation of the pharmaceutical formulation further comprising a coating is anticipated by the formulations that can be subjected to coating processes with a gastro-resistant film (Page 6, lines 9-14) and by the film coated resulting tablets of Example 1 (Page 7, lines 18-21) as taught by Villa.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 4-5, 9-10 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Villa et al. (WO 00/76481 A1).

The teaching of Villa is stated above.

Villa does not expressly teach in vitro release characteristics when measured in a model system using a USP Paddle System 2 operated at 37°C with stirring at 100 rpm.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition with 5-95% 5-ASA or mesalazine content in a lipophilic matrix granulate, as suggested by Villa, measure the in vitro release profile

of the mesalazine by using the standard USP protocol during the process of routine experimentation, and produce the instant invention.

One of ordinary skill in the art would do this because Villa measures the release of the active ingredient and discloses that lower than 30% of the active is released within the first hour in simulated enteric juice, an amount lower than 60% is released at the fourth hour and an amount lower than 90% is released at the eighth hour (Page 7, lines 22-27). One of ordinary skill in the art would use the established protocols in the USP for measuring the in vitro dissolution profile of mesalazine during the process of routine experimentation.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Regarding instant claim 4, the limitation of the pharmaceutical formulation having in vitro release characteristics such that at least 40% of the total amount of mesalazine in the formulation is released after 240 minutes would have been obvious over Example 1 where an amount lower than 60% of the active ingredient (5-ASA or mesalazine) is released at the fourth hour (Page 7, lines 22-25). The limitation of measuring the in vitro release characteristics in a model system using a USP Paddle System 2 operated at 37ºC with stirring at 100 rpm would have been obvious because one of ordinary skill in

the art would use the established protocols in the USP for measuring the in vitro dissolution profile of mesalazine during the process of routine experimentation.

Regarding instant claim 5, the limitations of the pharmaceutical formulation having in vitro release characteristics such that 5-25% of the total amount of mesalazine in the formulation is released after 15 minutes, such that 30-70% of the total amount of mesalazine in the formulation is released after 90 minutes, and such that 75-100% of the total amount of mesalazine in the formulation is released after 240 minutes would have been obvious over Example 1 where an amount lower than 30% of the active ingredient (5-ASA or mesalazine) is released within the first hour, an amount lower than 60% is released at the fourth hour, and an amount lower than 90% is released at the eighth hour, as taught by Villa (Page 7, lines 22-26). The limitation of the pharmaceutical formulation having in vitro release characteristics such that 30-70% of the total amount of mesalazine in the formulation is released after 90 minutes would also have been obvious over Example 2 where no more than 55% of the active ingredient (5-ASA or mesalazine) is released within two hours (Page 8, lines 9-12). One of ordinary skill in the art would find it obvious to modify the composition in order to achieve the desired dissolution profile during the process of routine experimentation. The limitation of measuring the in vitro release characteristics in a model system using a USP Paddle System 2 operated at 37°C with stirring at 100 rpm would have been obvious because one of ordinary skill in the art would use the established protocols in the USP for measuring the in vitro dissolution profile of mesalazine during the process of routine experimentation.

Regarding instant claim 9, the limitation of the pharmaceutical formulation further comprising a coating, wherein the ratio of the weight of the coating to the weight of the mesalazine is selected from the group consisting of 0.1-10%; 0.3-7%; 0.5-5%; 0.7-3%; 0.8-2%; and 0.9-1.5% would have been obvious over the film coating taught by Villa (Page 7, lines 18-21). One of ordinary skill in the art would manipulate the level of coating and vary the ratio of the weight of the coating to the weight of the active ingredient during the process of routine experimentation in order to achieve the desired controlled release. The recited ratios would have been obvious variants unless there is evidence of criticality or unexpected results.

Regarding instant claim 10, the limitation of the pharmaceutical formulation consisting essentially of mesalazine, a pharmaceutically acceptable binder and a coating would have been obvious over Example 1 with 5-ASA, Carbopol, hydroxypropylmethylcellulose and a film coating, as taught by Villa (Page 7, lines 5-21).

Regarding instant claim 26, the limitation of the pharmaceutical formulation having in vitro release characteristics such that 40-60% of the total amount of mesalazine in the formulation is released after 90 minutes would have been obvious over Example 1 where an amount lower than 30% of the active ingredient (5-ASA or mesalazine) is released within the first hour, an amount lower than 60% is released at the fourth hour, (Page 7, lines 22-26) and over Example 2 where no more than 55% of the active ingredient (5-ASA or mesalazine) is released within two hours (Page 8, lines 9-12), as taught by Villa. One of ordinary skill in the art would find it obvious to modify the composition in order to achieve the desired dissolution profile during the process of

routine experimentation. The limitation of measuring the in vitro release characteristics in a model system using a USP Paddle System 2 operated at 37°C with stirring at 100 rpm would have been obvious because one of ordinary skill in the art would use the established protocols in the USP for measuring the in vitro dissolution profile of mesalazine during the process of routine experimentation.

9. Claims 6 and 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Villa et al. (WO 00/76481 A1) in view of Augsburger et al. (US 2002/0177579 A1).

The teaching of Villa is stated above.

Villa does not expressly teach a pharmaceutical formulation having a similarity factor f_2 above 30 as compared to a standard formulation having in vitro release characteristics such that 12% of the total amount of mesalazine in the standard formulation is released after 15 minutes; 50% of the total amount of mesalazine in the standard formulation is released after 90 minutes; and 85% of the total amount of mesalazine in the standard formulation is released after 240 minutes.

Augsburger teaches an extended release granulation of a drug to achieve a specific drug release profile (Abstract). Augsburger also teaches that the similarity factor as defined by f_2 is used to determine whether two dissolution profiles are similar and that an f_2 between 50 and 100 suggests the two dissolution profiles are similar (Page 8, [0071] – [0072]).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition with 5-95% 5-ASA or mesalazine content in a lipophilic matrix granulate, as suggested by Villa, measure the in vitro release profile of the mesalazine by using the standard USP protocol during the process of routine experimentation, combine it with the calculation of a similarity factor in order to determine whether two dissolution profiles are similar, as suggested by Augsburger, and produce the instant invention.

One of ordinary skill in the art would do this because a similarity factor is routinely used in the art to determine the similarity of two dissolution profiles, as evidenced by the teaching of Augsburger.

Regarding instant claim 6, the limitation of the similarity factor would have been obvious over the calculation of a similarity factor in order to determine whether two dissolution profiles are similar, as suggested by Augsburger (Page 8, [0071] – [0072]). The limitations of the release profile (12% of the total amount of mesalazine in the standard formulation is released after 15 minutes; 50% of the total amount of mesalazine in the standard formulation is released after 90 minutes; and 85% of the total amount of mesalazine in the standard formulation is released after 240 minutes) would have been obvious over Example 1 where an amount lower than 30% of the active ingredient (5-ASA or mesalazine) is released within the first hour, an amount lower than 60% is released at the fourth hour, and an amount lower than 90% is released at the eighth hour, as taught by Villa (Page 7, lines 22-26). One of ordinary

skill in the art would find it obvious to modify the composition in order to achieve the desired dissolution profile during the process of routine experimentation.

Regarding instant claims 27-28, the limitations of the similarity factor f_2 above 40 and above 50 when compared to the standard formulation would have been obvious over the teaching by Augsburger that the similarity factor as defined by f_2 is used to determine whether two dissolution profiles are similar and that an f_2 between 50 and 100 suggests the two dissolution profiles are similar (Page 8, [0071] – [0072]).

10. Claims 11 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Villa et al. (WO 00/76481 A1) in view of Valducci (US 2002/0034541 A1).

The teaching of Villa is stated above.

Villa does not expressly teach that the pharmaceutical formulation is packed in a sachet.

Valducci teaches sachets and dispensers for granules or microgranules containing a mesalazine dosage ranging from 100 and 3000mg (Page 3, [0045]).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition with 5-95% 5-ASA or mesalazine content in a lipophilic matrix granulate, as suggested by Villa, combine it with the sachets that contain mesalazine, as suggested by Valducci, and produce the instant invention.

One of ordinary skill in the art would do this because sachets for granules of mesalazine are routinely used in the art, as evidenced by the teaching of Valducci.

Regarding instant claims 11 and 21, the limitation of the pharmaceutical formulation packed in a sachet would have been obvious over the sachets and dispensers for granules or microgranules containing a mesalazine dosage ranging from 100 and 3000mg, as taught by Valducci (Page 3, [0045]).

11. Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Villa et al. (WO 00/76481 A1) in view of Itoh et al. (US 5,194,464).

The teaching of Villa is stated above.

Villa does not expressly teach a pharmaceutical acceptable binder comprises Povidone.

Itoh teaches granules with active ingredients such as 5-ASA, and teaches additives such as binders, including polyvinylpyrrolidone (Col. 2, lines 31-39, lines 61-62, and Col. 3, lines 12-14).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition with 5-95% 5-ASA or mesalazine content in a lipophilic matrix granulate, as suggested by Villa, combine it with the granules of 5-ASA that also use polyvinylpyrrolidone as binder, as suggested by Itoh, and produce the instant invention.

One of ordinary skill in the art would choose polyvinylpyrrolidone from a finite number of predictable binders in granule formulations that contain actives such as 5-

ASA, with a reasonable expectation of success of producing a functional granular product.

Regarding instant claim 29, the limitation of Povidone as a pharmaceutically acceptable binder would have been obvious over the use of polyvinylpyrrolidone as a binder in the granule formulations that contain 5-ASA, as taught by Itoh (Col. 2, lines 31-39, lines 61-62, and Col. 3, lines 12-14).

12. Claims 29-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Villa et al. (WO 00/76481 A1) in view of Jurgens, Jr. et al. (US 5,316,772).

The teaching of Villa is stated above.

Villa does not expressly teach a pharmaceutical acceptable binder that comprises Povidone or a coating that comprises ethylcellulose.

Jurgens teaches a tablet core with mesalamine (5-ASA) and Povidone that is produced by wet granulation (Col. 8, Table 1). Jurgens also teaches a layer of coating with cellulose derivatives including ethylcellulose as coating agents (Col. 5, lines 30-34).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition with 5-95% 5-ASA or mesalazine content in a lipophilic matrix granulate, as suggested by Villa, combine it with the formulation of a wet granulation of 5-ASA that uses Povidone and ethylcellulose as a coating, as suggested by Jurgens, and produce the instant invention.

One of ordinary skill in the art would choose Povidone from a finite number of predictable binders in granule formulations and ethylcellulose as a coating agent, as

evidenced by Jurgens, with a reasonable expectation of success of producing a functional granular product that is coated.

Regarding instant claim 29, the limitation of Povidone as a pharmaceutically acceptable binder would have been obvious over the use of Povidone in a wet granulation of mesalamine, as taught by Jurgens (Col. 8, Table 1).

Regarding instant claim 30, the limitation of ethylcellulose as the coating would have been obvious over the ethylcellulose used as a coating agent by Jurgens (Col. 5, lines 30-34).

Conclusion

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Aradhana Sasan/
Examiner, Art Unit 1615

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